MEMORANDUM

Department Of Health and Human Services
Food and Drugs Administration
Center For Drug Evaluation and Research
Division of Over-the-Counter Drug Products (HFD-560)

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TO: Linda M. Katz, MD, MPH LMKatz
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FROM: Rosemarie Neuner, MD, MPH RN
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RE: Literature Search Submitted in Preparation for the September 2002 Advisory Committee Meeting on Over-The-Counter (OTC) Analgesic Safety Issues.

Background

In preparation for discussions on safety issues related to OTC analgesic products at the September 2002 Advisory Committee Meeting, the agency received a publication, copyrighted by the American Academy of Family Physicians, containing a list of references on gastrointestinal and renal adverse events associated with the use of OTC acetaminophen, aspirin, and nonsteroidal anti-inflammatory drugs (NSAIDs). From this reference list, 12 articles were reviewed. A listing of these 12 articles can be found at the end of this review in Appendix I. Six (6) of the 12 articles describe renal side effects. Of the remaining 6 references, 4 articles describe gastrointestinal adverse events. One of the two remaining articles is an editorial by Strom[11] and therefore was not reviewed. The twelfth article by Rahme[6] was not included in this review since it discusses the gastrotoxicity of prescription strength NSAIDs and not OTC products. The following is this medical officer's review of the 4 gastrointestinal articles followed by the 6 renal references.

Gastrointestinal References:

NSAID-induced gastrointestinal (GI) toxicity is well documented in the medical literature. Risk factors for developing NSAID-associated GI adverse events have been identified and include the following: age, gender, history of GI conditions, comorbid conditions, high doses, prolonged duration of use, type of NSAID, and concomitant therapy with another member of the drug class.[10] In his review article on the gastrotoxicity of OTC analgesics, Stiel[10] notes that despite the lower risk for developing GI toxicity associated with the ingestion of OTC NSAIDs, the increasing trend by consumers to self-medicate with these products theoretically should result in an increase in the number of NSAID-associated GI adverse events seen. Since the existing GI safety data for OTC NSAIDs is limited it is impossible to calculate the general public's attributable risk for the development of GI adverse events when using these products. In light of acetaminophen's favorable side-effect profile, the author concludes that it should be the initial analgesic of choice in the treatment of daily aches and pain.

The American College of Gastroenterology (ACG) conducted a case-control study that was designed to generate data that could be used to assess the risk of developing GI bleeding associated with the use of OTC doses of NSAIDs.[1] A total of 627 patients who had been entered into ACG's bleeding registry post- endoscopic examination for GI bleeding were matched to 590 control cases who had underwent endoscopy for reasons other than bleeding were interviewed regarding the recent use (i.e., within the week prior to the procedure) of analgesics, tobacco, alcohol and other factors. Analysis of the study data demonstrated that recent ingestion of aspirin, ibuprofen and other NSAIDs at OTC doses was associated with a 2-3 fold increase in the risk of GI bleeding. The study also showed that this risk increased with the size of the dose ingested, and that concomitant ingestion of alcohol doubled the risk for GI bleeding. No increase in risk for GI bleeding was demonstrated associated with the use of acetaminophen. The authors conclude that there is a need for additional research in this area particularly to determine if alcohol when combined with NSAIDs increases the risk of GI toxicity.

A matched case control study by Neutal et al[5] was designed to look at the risk of NSAID-associated GI adverse events in individuals with histories of alcoholism. A total of 1,083 cases who had been hospitalized for GI events generated from the Saskatchewan Health Databases were matched to a control group comprised of 14,754 individuals who had never been hospitalized for such problems. Further examination of the study cohort revealed only 54 cases (5%) versus 273 cases (1.9%) of the matched controls had a history of alcoholism. The calculated odds ratio (OR) for either NSAID use or alcohol use alone associated with GI events was found to be 2.9 versus an OR of 10.2 when both risk factors were simultaneously present ($p<0.05$). The OR for GI events associated with OTC ibuprofen and naproxen but without alcohol use was found to be 1.9 versus an OR of 6.5 when these drugs were taken with chronic alcohol ingestion ($p<0.05$). The authors conclude that further research is needed to evaluate the concurrent risk of alcohol ingestion with NSAIDs.

The last article by Sorenson et al[9] was an observational cohort study that evaluated the risk of upper GI bleeding associated with the use of low-dose aspirin. The study cohort of 207 patients recently treated for upper GI bleeds and who admitted exclusively using low-dose aspirin were identified from a population-based prescription database and hospital discharge registry in Denmark that contained 27,694 users of low-dose aspirin. Based on the data generated from the study cohort group, the standardized incidence rate ratio for upper GI bleeds was calculated to be 2.6 in females and 2.8 in males (95% confidence interval (CI), 2.2-2.9). The authors note that the standardized incidence rate ratio for combined use of low-dose aspirin and another NSAID was 5.6 (95% CI, 4.4-7.0). The study did not demonstrate any reduction in the risk for GI bleeding associated with enteric coated low-dose aspirin (standardized incidence rate ratio: 2.6; 95% CI, 2.2-3.0) versus that of noncoated low-dose aspirin (standardized incidence rate ratio: 2.6; 95% CI, 1.8-3.5). Based on these findings, the authors conclude that there is an increase risk for upper GI bleeding associated to the use of low-dose aspirin. This risk increases when low-dose aspirin is combined with other NSAIDs, and is not diminished by the use of enteric-coated products. Thus, the potential benefit of prophylactic aspirin therapy for cardiovascular disease may be decreased by the co-morbid risks associated with GI bleeding.

Renal References:

Since renal function is dependent upon hemodynamic mechanisms that are regulated by renal prostaglandins synthesized by the cyclooxygenase pathway, nonsteriodal anti-inflammatory drugs such as ibuprofen can potentially alter renal function by their ability to inhibit renal prostaglandin production. In a cross-over study, Farquhar et al[3] looked at the effects of 4 g/day of acetaminophen versus 1,200 mg/day of over-the-counter ibuprofen versus placebo had on the renal function of 12 healthy, young (25 years $\pm$ 1 year) men and women. Following the baseline measurement of various renal parameters, study subjects were progressively subjected to salt restriction, dehydration and exercise, which have all been previously shown to produce transient reductions in renal function, while taking one of the assigned treatments. The results generated from this study demonstrated that these combined stressors produced major decreases in effective renal plasma flow, glomerular filtration rate (GFR) and sodium excretion. There was a statistically significant decrease in postexercise GFR measurements following treatment with ibuprofen as compared to placebo (p-value < 0.05). This study also demonstrated that treatment with ibuprofen in postexercise sodium and volume depleted states resulted in small but statistically significant decreases in the subjects GFR. No adverse effects on renal function post stressors was noted in subjects when treated with acetaminophen. Although acetaminophen is a member of the NSAID-class of drugs, it does not inhibit renal prostaglandins, and therefore does not cause the cardiovascular and renal side effects (i.e., fluid and salt retention, hypertension, and acute renal failure) associated with other members of this drug class.[12]

In his review article on the renal and related cardiovascular effects of first generation and COX-specific NSAIDs and non-NSAID analgesics, Whelton[12] discusses the various NSAID-associated renal syndromes which range from salt and fluid retention to acute renal failure and renal papillary necrosis that have been documented in the literature. Although he notes that most of the NSAID-associated nephrotoxic syndromes are reversible after stopping the drug, some individuals will require supportive dialysis while their kidneys recover. The author also discusses the results of 2 large meta-analyses that showed NSAID-induced increases in blood pressure in treated hypertensive patients due to the diminished efficacy of antihypertensive drugs. He notes in his review that these meta-analyses excluded data related to elderly patients, but states that there is sufficient published data to conclude that the use of NSAIDs increase the risk of hypertension in this population. Whelton[12] concludes that while acetaminophen should be the analgesic initially recommended to populations at risk for the development of NSAID-associated nephrotoxicity, consideration of the various risk factors for the development of NSAID renal toxicity (i.e., advanced age, diabetes, dehydration especially in children, and underlying hepatic or renal disease) needs to be used when recommending an analgesic.

Since many of the studies in analgesic nephropathy are know to be methodologically flawed, renal and drug usage data captured by the case-controlled Physicians' Health Study was examined to determine if an increase risk for developing chronic renal disease was associated with the use of analgesic agents.[7] Of the 11,032 subjects who participated in this cohort study, a total of 460 men (4.2%) were found to have elevated serum creatinine levels while 1,258 men (11.4%) had diminished creatinine clearances. The authors noted that in participating men who used analgesics even in excess of 2,500 pills over the 14 years of the study, their mean creatinine levels and clearances were similar to those who did not take analgesics. The relative risks (RR) for elevated creatinine levels associated with the ingestion of $\geq$ 2,500 pills after adjusting via multivariate analysis for age, body mass index, hypertension, hypercholesterolemia, diabetes, cardiovascular disease, physical activity, and the use of other analgesics were found to be as follows: acetaminophen – RR: 0.83 (95% confidence interval [CI], 0.50-1.39; P for trend = 0.05); aspirin – RR 0.98(95% CI, 0.53-1.81; P for trend = 0.96); other NSAIDs - RR:1.07 (95% CI, 0.71-1.64; P for trend = 0.86). Further analysis of the data failed to demonstrate an association between analgesic use and reduced creatinine clearance in the cohort studied. Thus the authors concluded that based on the findings of this cohort study, moderated analgesic use in men who were initially healthy at the start of the study was not associated with an increase in risk for renal disease.

Fored et al[3] conducted a retrospective, matched, case-controlled study in Sweden that was designed to overcome the problems that had plagued previous analgesic nephropathy studies. In this study, 926 prospective subjects were identified from monthly laboratory listings of abnormal renal tests that defined early chronic renal failure as a serum creatinine greater than 3.4 mg per deciliter in males and 2.8 mg per deciliter in females. Renal transplant patients, or individuals who had prerenal (i.e., renal disease secondary to heart failure) or postrenal (i.e., post-obstructive renal disease) etiologies for their renal failure were excluded from the study. Following confirmation of prospective subjects' renal disease by a follow-up serum creatinine 3 months after the first test, they were matched by age and sex to 998 normal controls that were randomly selected from the Swedish Population Register. All participating subjects were then interviewed by trained study personal using a study booklet with color pictures of packaging from 78 major brands of analgesics containing acetaminophen or phenacetin that were sold in Sweden during the time period from 1960 to 1996. Study data regarding consumption of analgesics, including duration, dose, and patterns of drug use was thus collected and used to calculated via logistic-regression models the relative risks of disease-specific types of chronic renal failure associated with the use of various analgesics. The results of this study revealed that 86% of the renal failure patients and 75% of the controls used nonnarcotic analgesics regularly. (Note: "Regular use" of an analgesic was predefined by the authors at the study onset as at least twice a week for 2 months.) Thirty-seven percent (37%) and 25% of the renal failure subjects admitted to regularly using aspirin and acetaminophen respectively, as compared to 19% and 12% respectively of the control group. In subjects who regularly used either aspirin or acetaminophen singlely, the relative risk for developing renal failure was calculated to be 2.5 times that of nonusers from any cause. Author's Table 1 shown below, lists the calculated odds ratios with 95% confidence interval for developing chronic renal failure associated with regular use of acetaminophen and aspirin for the subjects entered in this study.

Author's Table 1 – Odds Ratio for Chronic Renal Failure Associated with the Lifetime Use of Either Acetaminophen or Aspirin Among Subjects Who Did Not Use the Other Analgesic Regularly*

Variable	Acetaminophen Use Odds Ratio (95% CI)	Aspirin Use Odds Ratio (95% CI)
Never used	1.0	1.0
Ever Used	1.3 (1.0-1.6)	1.5(1.2-1.8)
Use or Used Regularly	2.5 (1.7-3.6)	2.5(1.9-3.3)
Cumulative Dose :**		
1-99 g	1.2(0.9-1.5)	1.4(1.1-1.7)
100-499 g	1.3(0.9-1.8)	1.6(1.2-2.10
>500 g	3.3(2.0-5.5)	1.9(1.3-2.9)

*The odds ratios have been adjusted for age, sex, level of education, smoking status, use or nonuse of other analgesics, and the interaction between aspirin use and acetaminophen use. Regular use was defined as the use of at least two tablets per week for a period of 2 months or longer.

**P-value <0.001 for the trend toward greater risk with increasing cumulative doses of acetaminophen; P-value =0.01 for the trend toward greater risk with increasing cumulative doses of aspirin.

As demonstrated in the preceding table, Author's Table 1, the relative risks (i.e., odds ratio) increased with increasing cumulative dose, and the magnitude of the increase was higher with acetaminophen than aspirin use. The authors also looked at the association between analgesic use and the risk of renal failure in 324 patients with diabetes and chronic renal failure as compared to 67 control subjects with diabetes. The calculated relative risk associated with regular acetaminophen use in the absence and presence of regular aspirin use was 4.0 (95% CI, 1.0-16.1) and 2.4(95% CI, 0.7-8.1) respectively. The calculated relative risk associated with regular aspirin use in the absence and presence of regular acetaminophen use was 1.4(95% CI, 0.7-3.1) and 0.6(95% CI, 0.1-3.2) respectively.

A review article by Elseviers et al[2] discusses both the epidemiological and experimental evidence that has been published in support of the theory that analgesic nephropathy results from the prolonged use of combination analgesic compounds containing caffeine and/or codeine. The authors note that the evidence in support of single analgesic agents causing this disorder was both limited and inconsistent in nature. Attempts to further clarify the causal relationships involved in the development of analgesic nephropathy have lead researchers such as Rocha et al[8] to study the toxic effects of these drugs in animal models. Based on results generated from their research in which mouse inner medullary collecting duct tissue was exposed to a variety of nonnarcotic analgesic drugs (i.e., salicylic acid, aspirin, acetaminophen, caffeine, indomethacin, and NS398), the authors concluded that all of the drugs tested were directly toxic to mouse renal tissue since the drugs caused apoptosis of the exposed cells. Their study also demonstrated that rapidly proliferating cell lines were affected more severely by the analgesics tested than slowly proliferating ones. This was particularly true of the combination of caffeine and acetaminophen. The authors suggest that the increase in toxicity associated with the combination of caffeine and acetaminophen is possibly related to caffeine's potentiation of acetaminophen's toxic effects due to the former's ability to inhibit cellular repair of damaged DNA. Rocha et al[8] also noted that apoptosis of mouse renal cell tissue following exposure to dose-dependent inhibitors of cyclooxygenase (COX) (i.e., indomethacin and NS398) occurred only when the concentrations of these drugs were well above the levels needed to inhibit cyclooxygenase in the animal model studied. Thus the results from this study supports the hypothesis by Elseviers et al[2] that analgesic combinations involving caffeine are more likely to be responsible for the development of analgesic nephropathy.

Summary

The GI literature reviewed above reinforces what is already known about the gastrotoxicity profile of NSAIDs in general. Review of the renal literature demonstrates that normal individuals are unlikely to develop renal failure due to the chronic use of analgesics but those with underlying risk factors such as advanced age, diabetes, dehydrated states (especially in children), and underlying hepatic or renal disease are at an increase risk.